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(21) International Application Number: PCT/DK98/00301 (22) International Filing Date: 2 July 1998 (02.07.98) (30) Priority Data: 60/052,022 9 July 1997 (09.07.97) US 0922/97 11 August 1997 (11.08.97) DK (71) Applicants (for all designated States except US): NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK). CENTRAL DRUG RESEARCH INSTITUTE [IN/IN]; Chatrar Manzil, Lucknow - 226 001 (IN). (72) Inventors; and (75) Inventors/Applicants (for US only): HAJELA, Kanchan [IN/IN]; C-380, Sector B, Mahanagar, Lucknow - 220 006 (IN). PANDEY, Jaya [IN/IN]; D/o Shri. L. N. Pandey, New Defence Colony, Utrathia, Lucknow - 226 002 (IN). DHAR, Janak, Dulari [IN/IN]; R.No.4, HAL Guest House, HAL Executive Township, Faizabad Road, Lucknow - 226 016 (IN). RAY, Suprabhat [IN/IN]; 16/3.Kha, Sarojini Naidu Marg, Behind Masonic Lodge, Lucknow - 226 001 (IN). LABROO, Virender, Mohan [IN/US]; 2814-163rd Place S.E., Mill Creek, WA 98012 (US).	(74) Common Representative: NOVO NORDISK A/S; Corporate Patents, Novo Allé, DK-2880 Bagsvaerd (DK). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: DL-2,3-DIARYL-2H-1-BENZOPYRANS		
(57) Abstract		
<p>The present invention relates to therapeutically active 2,3-diaryl-2H-1-benzopyrans, a method of preparing the same and to pharmaceutical compositions comprising the compounds. The novel compounds are useful in the prevention or treatment of estrogen related diseases or syndromes.</p>		

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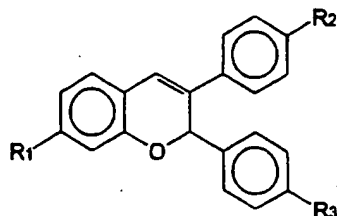
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dl-2,3-Diaryl-2H-1-benzopyrans

The present invention relates to optically active *d*- and *l*-isomers of *dl*-2,3-diaryl-2H-1-benzopyran and its derivatives, their preparation by the process of resolution, preparation of pharmaceutical compositions containing such isomers as active ingredients and their use as contraceptives, in the treatment and prophylaxis of breast cancer, osteoporosis, hypercholesteremia, endometriosis, vasoconstriction and endometrial disorders.

2,3-Diaryl-2H-1-benzopyrans have recently emerged as a novel group of non-steroidal compounds which are anti-estrogenic and possess significant activity against egg implantation and breast cancer (see Kapil et al., U.S. Pat. No. 5,254,568 dt. Oct.19, 1993; Saeed et al., *J. Med. Chem.*, **33**, 3210-3216, 1990; Sharma et al., *J. Med. Chem.*, **33**, 3216-3222, 3222-3229,1990). They have also been shown to be effective in the treatment of bone loss due to osteoporosis and other conditions, including post- menopausal osteoporosis and glucocorticoid -related osteoporosis, Paget s disease, hyperparathyroidism, hypercalcemia of malignancy and other conditions characterized by excessive rates of bone resorption and/ or decreased rates of bone formation (see Labroo et al., U.S. Pat. No. 5,389,646 dt. Feb.14, 1995). Further, they are also useful for lowering serum cholesterol (see Eli Lilly & Company, Eur. Pat. No. 0,652,006 A1 dt. Nov.2, 1994). Indian Patent Appl. Nos. 173335, 173336, 173337 and 1141/DEL/91 describe the process for the preparation of *dl*-2,3-diaryl-2H-1-benzopyran and derivatives thereof. The invention provides compounds of the formula



wherein R¹ and R² which may be the same or different are each H, OH, linear or branched chain alkyl or alkoxy of 1 to 17 carbon atoms, linear or branched chain acyloxy of 2 to 18 carbon atoms or a halide group and R³ is a tertiary amino alkoxy group such as O(CH₂)_nNR⁴R⁵ wherein R⁴ and R⁵ are same or different, linear or
5 branched chain alkyl substituents of 1-18 carbon atoms or a cyclic ring containing 2 - 10 carbon atoms containing the N atom.

There are several preferred embodiments. In one preferred embodiment R¹ and R² are each independently H, OH or C₁₋₄-alkoxy. Other preferred embodiments include (i) R¹ being H or (ii) R¹ and R² each being an acyl, alkyl, alkoxy or a halide
10 group. R³ is preferably a 2-piperidinoethoxy group.

With the increasing appreciation that the enantiomers of a chiral drug can differ in their biological activity, pharmacokinetically and/or pharmacodynamically, there is considerable interest in the resolution of such molecules into their pure enantiomeric forms. As 2,3-diaryl-2H-1-benzopyran and its derivatives evince potent antiestrogenic, antiimplantation, antibreast cancer, antiosteoporosis and serum cholesterol
15 lowering activities, the applicants have affected additional research by affecting the resolution of racemic compound into its optically active *laevo* (l) and *dextro* (d) isomeric forms. The achieved compounds particularly the l-isomer exhibits increased anti-implantation and antiestrogenic activities over the known dl-isomer.

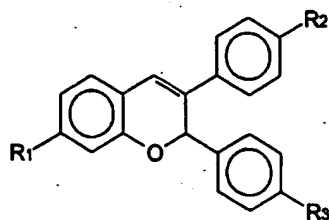
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The present invention therefore provides as new compounds *laevo* and *dextro* forms of dl-2,3-diaryl-2H-1-benzopyrans specifically:

d-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran,
l-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran,
25 l-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-(4-hydroxyphenyl)-2H-1-benzopyran,
l-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-phenyl-7-methoxy-2H-1-benzopyran,
l-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-(4-hydroxyphenyl)-7-hydroxy-2H-1-benzopyran,
l-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-(4-methoxyphenyl)-2H-1-benzopyran,
30 d-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-(4-methoxyphenyl)-2H-1-benzopyran.

The new compounds correspond to the general formula

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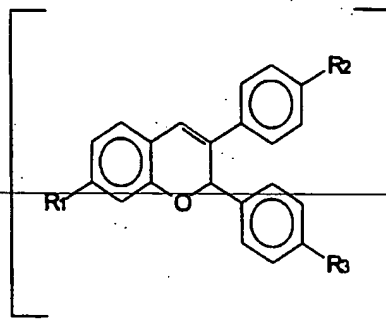


wherein R^1 , R^2 and R^3 have the meanings as stated above.

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The invention includes within its scope the optically active *l*-acid and *d*-acid salts of the new compounds referred to above. These salts are characterized by the general formula

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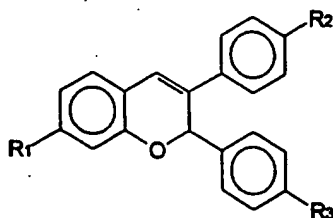
wherein X denotes the optically active anion and R^1 , R^2 and R^3 have the meanings as stated above.

25

According to a preferred feature, the present invention provides a process for the preparation of optically active *l* and *d* isomers of *dl*-2,3-diaryl-2H-1-benzopyrans and optically active salts thereof which comprises reacting a

dl-2,3-diaryl-2H-1-benzopyran compound of the general formula

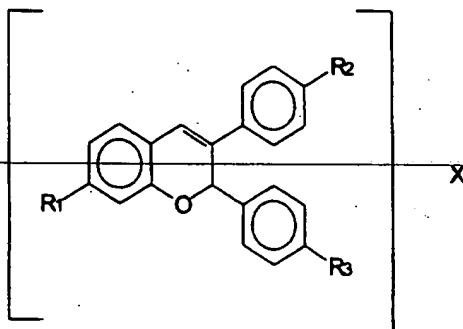
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wherein R^1 and R^2 which may be the same or different are each H, OH, linear or branched chain alkyl or alkoxy of 1 to 17 carbon atoms, linear or branched chain acyloxy of 2 to 18 carbon atoms or a halide group and R^3 is a tertiary amino alkoxy group such as $O(CH_2)_nNR^4R^5$ wherein R^4 and R^5 are same or different, linear or branched chain alkyl substituents of 1-18 carbon atoms or a cyclic ring containing 2 - 10 carbon atoms containing the N atom with an optically active acid in a protic solvent to produce optically active salt of the formula

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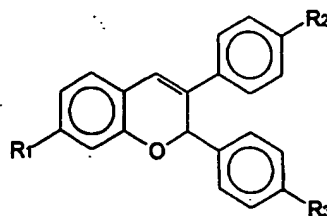


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wherein X denotes the optically active acid anion, subjecting the reaction mixture to repeated fractional crystallization to obtain the said salt in crystalline form and subjecting the crystalline salt to alkaline hydrolysis to obtain the desired isomer.

According to a further feature, the invention provides a process for the preparation of *l*-2-4-(2-(1-piperidino)ethoxy)phenyl-3-phenyl-2H-1-benzopyran of the general formula

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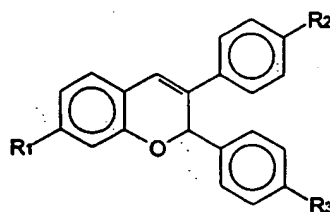


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wherein R^1 , R^2 , R^3 have the meanings stated herein and optically active *l*-acid salts thereof, which comprises reacting

dl-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran of the general

10 formula

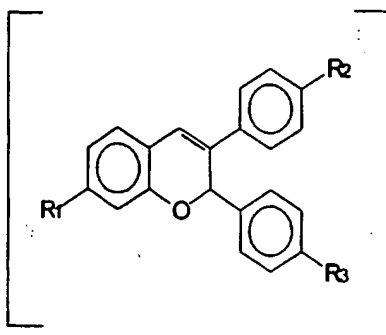


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wherein R^1 , R^2 , R^3 have the meanings stated above with an optically active *l*-acid in a protic solvent to produce on fractional crystallization of the reaction mixture

l-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran *l*-acid salt of the

20 general formula



X

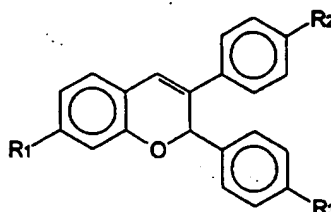
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wherein X denotes the optically active anion and R^1 , R^2 , R^3 have the meanings stated above and subjecting the said crystalline salt to alkaline hydrolysis to obtain the desired *l*-isomer.

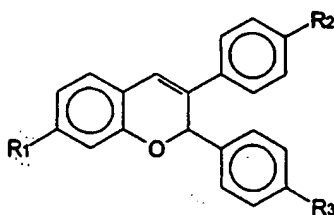
- 5 According to a still further feature, the invention provides a process for the preparation of *d*-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran of the general formula

10



- 15 wherein R^1 , R^2 and R^3 have the meanings stated as above and optically active *d*-acid salt thereof which comprises reacting
dl-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran of the general formula

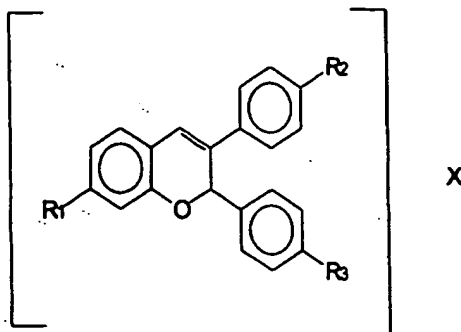
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- 25 wherein R^1 , R^2 , R^3 have the meanings as stated above with an optically active *d*-acid in a protic solvent to produce on fractional crystallization of the reaction mixture
d-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran *d*-acid salts of the general formula

30

5



10 wherein X denotes the optically active anion and R^1 , R^2 , R^3 have the meanings stated as above and subjecting the said crystalline salt to alkaline hydrolysis to obtain the desired *d*-isomer.

The preferred optically active *l*-acid is di-*p*-toluoyl-*l*-tartaric acid while the preferred optically active *d*-acid is di-*p*-toluoyl-*d*-tartaric acid monohydrate.

15 Examples of the protic solvents which may be employed in the reaction include ethanol or methanol.

According to yet another embodiment the invention provides a post-coital antifertility composition comprising as active ingredient

20 *l*-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran or an optically active acid derivative thereof in combination with a pharmaceutically acceptable carrier or excipient thereof. Examples of the carriers or excipients with which the active ingredient may be combined to provide the above-mentioned composition include starch, dicalcium phosphate and calcium stearate and combinations of any of these.

25 The novel *l*-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran was found to be two folds more active as an antifertility agent in female albino rats as compared to the corresponding *dl*-compound in a single day post-coital oral administration schedule.

30 The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable

dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen useful in the prevention or treatment of estrogen related diseases or syndromes it may frequently be necessary to begin with a dosage of from about 20 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

10 The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

15

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. The formulations may also include wetting agents, emulsifying and suspending agents, preserving

agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

5

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

10

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

15

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

20

Generally, the compounds are dispensed in unit form comprising from about 0.1 to about 100 mg in a pharmaceutically acceptable carrier per unit dosage.

A typical tablet, appropriate for use in this method, may be prepared by conventional tableting techniques and contains:

25

Active compound	5.0 mg
Lactosum	67.8 mg Ph.Eur.
Avicel®	31.4 mg
Amberlite®	1.0 mg
30 Magnesium stearas	0.25 mg Ph. Eur.

The compounds according to this invention may be suitable for administration to an animal. Such animals include both domestic animals, for example livestock, laboratory animals, and household pets, and non-domestic animals such as wildlife. More preferably, the animal is a vertebrate. Most preferably, a compound according to this invention shall be administered to a mammal. It is especially preferred that the animal is a domestic mammal or a human. The most preferred mammal is a human. For such purposes, a compound of this invention may be administered as a feed additive or in bulk form.

The preparation of the novel compounds and its derivatives are described in the following non-limitative examples.

Example I

***l*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran di-*p*-toluoyl-*l*-tartrate**

dl-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran and di-*p*-toluoyl-*l*-tartaric acid in 1:1 equivalent molar ratio were dissolved by warming in distilled ethanol and the mixture stirred for 3 hrs. Excess of ethanol was removed and the residue allowed to stand overnight to get crystals of *l*-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran di-*p*-toluoyl-*l*-tartrate, m.p. 126° C, $[\alpha]_D^{20} = -72.2$ (c 1 in EtOH).

Example II

***l*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran**

The *l*-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran di-*p*-toluoyl-*l*-tartrate salt obtained from the example I was hydrolyzed by dissolving it in ethyl acetate and treating it with aqueous alkali. The organic layer was washed with water to neutral, dried over anhydrous sodium sulphate and concentrated to
5 yield colorless crystalline
l-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran, m.p. 75° C, $[\alpha]^{20}_D = -34.3$ (c 1 in EtOH).

10

Example III

***d*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran
di-*p*-toluoyl-*d*-tartrate**

15 *dl*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran and di-*p*-toluoyl-*d*-tartaric acid monohydrate in 1:1 equivalent molar ratio were dissolved in ethanol and the mixture stirred for 3 hrs. Excess of ethanol was removed and the residue allowed to stand overnight to get crystals of pure

20 *d*-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran
di-*p*-toluoyl-*d*-tartrate as colorless solid m.p. 132° C, $[\alpha]^{20}_D = +72.2$ (c 1 in EtOH).

Example IV

25 ***d*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran**

The *d*-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran di-*p*-toluoyl-*d*-tartrate salt obtained from example III was hydrolyzed by dissolving the salt in ethyl acetate and treating it with aqueous alkali. The organic layer was
30 washed with water to neutral, dried over anhydrous sodium sulphate and concentrated to yield colorless, crystalline solid m.p. 69° C, $[\alpha]^{20}_D = +34.3$ (c 1 in EtOH).

Example V

5 ***l*-2-(4-(2-(1-Piperidino)ethoxy)phenyl-3-(4-methoxyphenyl)-2H-1-benzopyran di-p-toloulyl-*l*-tartrate**

dl-2-(4-(2-(1-Piperidino)ethoxy)phenyl-3-(4-methoxyphenyl)-2H-1-benzopyran of the general formula I and di-p-toloulyl-*l*-tartaric acid in 1:1 equivalent molar ratio were
10 dissolved by warming in distilled ethanol and the mixture stirred for 3 hrs. Excess of ethanol was removed and the residue allowed to stand overnight to get the crystals of *l*-2-(4-(2-(1-piperidino)ethoxy)phenyl-3-(4-methoxyphenyl)-2H-1-benzopyran di-p-toloulyl-*l*-tartrate, m.p. 122°C, $[\alpha]^{20}_D = -83.9$ (c 1 in EtOH).

15

Example VI

***l*-2-(4-(2-(1-Piperidino)ethoxy)phenyl-3-(4-methoxyphenyl)-2H-1-benzopyran**

20 The *l*-2-(4-(2-(1-piperidino)ethoxy)phenyl-3-(4-methoxyphenyl)-2H-1-benzopyran di-p-toloulyl-*l*-tartrate salt obtained from example V was hydrolysed by dissolving it in ethyl acetate and treating it with aqueous alkali. The organic layer was washed with water to neutral, dried over anhydrous sodium sulphate and concentrated to yield colorless crystalline *l*-2-(4-(2-(1-piperidino)ethoxy)phenyl-3-(4-methoxyphenyl)-2H-1-
25 benzopyran, m.p. 92°C, $[\alpha]^{20}_D = -40.3$ (c 1 in EtOH).

Example VII

***d*-2-(4-(2-(1-Piperidino)ethoxy)phenyl-3-(4-methoxyphenyl)-2H-1-benzopyran di-p-toloulyl-*d*-tartrate**
30

dl-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-(4-methoxyphenyl)-2H-1-benzopyran and di-
p-toloulyl-*d*-tartaric acid monohydrate in 1:1 equivalent molar ratio were dissolved in
ethanol and the mixture stirred for 3 hrs. Excess of ethanol was removed and the
residue allowed to stand overnight to get crystals of pure *d*-2-(4-(2-(1-
5 piperidino)ethoxy)phenyl)-3-(4-methoxyphenyl)-2H-1-benzopyran di-p-toloulyl-*d*-
tartrate as colorless solid, m.p. 128°C, $[\alpha]^{20}_D = +83.9$ (c 1 in EtOH).

Example VIII

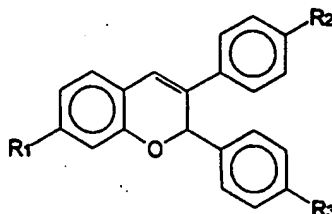
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***d*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-(4-methoxyphenyl)-2H-1-benzopyran**

The *d*-2-(4-(2-(1-piperidino)ethoxy)phenyl)-3-(4-methoxyphenyl)-2H-1-benzopyran di-
p-toloulyl-*d*-tartrate salt obtained from example VII was hydrolysed by dissolving the
15 salt in ethyl acetate and treating it with aqueous alkali. The organic layer was
washed with water to neutral, dried over anhydrous sodium sulphate and concen-
trated to yield colorless crystals, m.p. 89°C, $[\alpha]^{20}_D = +40.3$ (c 1 in EtOH).

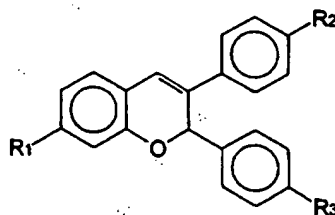
Claims

1. An *L*-isomer of a compound of the formula



wherein R^1 and R^2 which may be the same or different are each H, OH, linear or branched chain alkyl or alkoxy of 1 to 17 carbon atoms, linear or branched chain acyloxy of 2 to 18 carbon atoms or a halide group and R^3 is a tertiary amino alkoxy group such as $O(CH_2)_nNR^4R^5$ wherein R^4 and R^5 are same or different, linear or branched chain alkyl substituents of 1-18 carbon atoms or a cyclic ring containing 2 - 10 carbon atoms containing the N atom.

2. A *D*-isomer of a compound of the formula



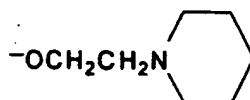
wherein R^1 , R^2 , and R^3 have the meanings as stated as above in claim 1.

3. Compounds as claimed in claim 1 and 2 in which R^1 and R^2 each independently are H, OH, halide, or C_{1-4} -alkoxy.

4. Compounds as claimed in claim 1 and 2 in which R¹ is H.

5. Compounds as claimed in claim 1 and 2 in which R³ is

5



6. *l*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-(4-hydroxyphenyl)-2H-1-benzopyran according to claim 1.

10

7. *l*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-phenyl-7-methoxy-2H-1-benzopyran according to claim 1.

8. *l*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-(4-hydroxyphenyl)-7-hydroxy-2H-1-benzopyran according to claim 1.

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9. *l*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-(4-methoxyphenyl)-2H-1-benzopyran according to claim 1.

10. *l*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran according to claim 1.

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11. *d*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-phenyl-2H-1-benzopyran according to claim 2.

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12. *d*-2-(4-(2-(1-Piperidino)ethoxy)phenyl)-3-(4-methoxyphenyl)-2H-1-benzopyran according to claim 2.

13. A pharmaceutical composition which comprises an effective dose of a compound according to claim 1 and 2 and a pharmaceutically acceptable carrier or diluent.

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14. The use of a compound according to claim 1 and 2 for the preparation of a medicament for prevention or treatment of estrogen related diseases or syndromes.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00301

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 311/60, A61K 31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5254568 A (RANDHIR S. KAPIL ET AL), 19 October 1993 (19.10.93) --	1-14
A	WO 9310741 A2 (ENDORECHERCHE INC.), 10 June 1993 (10.06.93) --	1-14
A	WO 9626201 A1 (ENDORECHERCHE), 29 August 1996 (29.08.96) -----	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

* "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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* "&" document member of the same patent family

Date of the actual completion of the international search

7 October 1998

Date of mailing of the international search report

13-10-1998

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INTERNATIONAL SEARCH REPORT
Information on patent family members

27/07/98

International application No.
PCT/DK 98/00301

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WO 9626201 A1	29/08/96	AU 4660696 A BR 9607259 A CA 2212856 A CN 1181077 A EP 0811006 A FI 973426 A IL 117177 D NO 973836 A PL 321892 A	11/09/96 30/12/97 29/08/96 06/05/98 10/12/97 20/10/97 00/00/00 20/08/97 22/12/97

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